Remarks

Amendments to the Claims

Claim 10 has been amended to delete "preventing," "inhibited," and "prevented" and to recite instead "reducing" neuronal cell death. This amendment is supported in par. 47 of the specification: "Specific biological antagonists of NMs can also be used to therapeutic benefit. For example, antibodies, T cells specific for an NM, antisense to an NM, and ribozymes specific for an NM can be used to restrict, inhibit, reduce, and/or diminish neuronal cell death (up-regulated genes or proteins)." Claim 10 also has been amended to delete an extraneous recitation of "NM."

The amendments do not add new matter.

Objection to the Drawings

The Office Action objects to the drawings because they are "lists of genes" but are referred to in the specification as "Figures." To advance prosecution, Figures 1-9 have been deleted and their contents presented in Tables 1-9. Corresponding amendments have been made to the specification to refer to "tables" rather than "figures."

Please withdraw the objection.

Rejection of Claims 10 and 12-19 Under 35 U.S.C. § 112 ¶ 2

Claims 10 and 12-19 stand rejected under 35 U.S.C. § 112 ¶ 2. Applicants respectfully traverse the rejection.

The Office Action contends the term "preventing" is unclear and finds no antecedent basis for the recitation "inhibited" in claim 10. To advance prosecution independent claim 10

has been amended to delete the terms "preventing" and "inhibited" and to recite instead "reducing" neuronal cell death.

Please withdraw the rejection.

Rejection of Claims 10 and 12-19 Under 35 U.S.C. § 112 ¶ 1

Claims 10 and 12-19 stand rejected under 35 U.S.C. § 112 ¶ 1 as neither described nor enabled. Applicants respectfully traverse the rejections.

Written Description

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). Thus, the first step in a written description inquiry is to construe the claims at issue. *Vas-Cath*, 935 F.2d at 1560, 19 U.S.P.Q.2d at 1116.

Independent claim 10 is directed to a method of reducing neuronal cell death in a mammal. The method comprises administering to the mammal a nucleic acid molecule comprising a coding sequence for a neuronal marker (NM) protein. The Office Action contends that claim 10 encompasses "a genus of unspecified 'neuronal markers' . . . ." Office Action at page 4 ¶ 1. To the contrary, claim 10 explicitly recites a Markush group of proteins from which the NM protein must be selected.

Moreover, neither the NM proteins nor the nucleic acid molecules encoding them are new. For example, a coding sequence for androgen binding protein, which is the elected species, has been known in the art since at least 1993. See Attachment 1, which is the coding sequence for rat androgen binding protein (GenBank Accession No. M15034). To demonstrate possession

of the claimed method, it is not necessary for Applicants to demonstrate possession of the old elements of the claimed method, *i.e.*, the known recited proteins and their coding sequences. It is black letter law that a specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

What is required to satisfy the written description requirement depends on the nature of the invention claimed. *In re DiLeone*, 436 F.2d 1404, 1405, 168 U.S.P.Q. 592, 593 (C.C.P.A. 1971). The claimed method is based on the identification of the known proteins as neuronal markers because their expression is altered after axiotomy, not on the identification of these proteins *per se* (see par. [50]). The specification amply describes the identification of these proteins as neuronal markers and therefore sufficiently describes the claimed method.

Applicants respectfully request withdrawal of the rejection.

Enablement

The enablement requirement of 35 U.S.C. § 112, first paragraph states that a patent specification must teach a person skilled in the relevant art how to make and use the invention claimed. The proper standard for determining whether the present specification meets the enablement requirement is whether any experimentation which may be needed to practice the methods of claims 10 and 12-19 is undue or unreasonable. *In re Wands*, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

The U.S. Patent and Trademark Office has the initial burden to establish a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). To make a *prima facie* case of non-enablement using this standard, an Examiner must properly construe the claims and must weigh all the evidence and establish a reasonable basis to question the enablement provided in the

specification for the claimed invention. M.P.E.P. §§ 2164.04 and 2164.05, 8th ed., August, 2005. In the present application, a *prima facie* case of non-enablement has not been made. The weight of evidence, including the teachings of the specification and the prior art – and including the references cited in the rejection – favors the conclusion that claims 10 and 12-19 are enabled. This evidence is discussed below in connection with each of the *Wands* factors.

The nature of the invention and the breadth of the claims

The rejected claims are directed to a method of reducing neuronal cell death in a mammal. The method comprises administering to the mammal a nucleic acid molecule comprising a coding sequence for a neuronal marker (NM) protein selected from a recited group of proteins.

The Office Action misconstrues the scope of claims 10 and 12-19. First, the Office Action characterizes the claims as "encompass[ing] a genus of nucleic acid molecules to prevent any human disorder characterized by neuronal cell death." Office Action at page 9, lines 7-8. The claims recite administration of the nucleic acid molecule to a mammal and are therefore not limited to human administration. The claimed methods encompass but do not require preventing a disorder characterized by neuronal cell death.

Second, the Office Action consistently misconstrues the claims as requiring use of a non-viral vector.[1] The claims are not so limited. The claims recite "administering to the mammal a nucleic acid molecule comprising a coding sequence . . . ." See par. [46]:

[1] *See, e.g.*, page 9, lines 5-6 ("Regarding the claimed invention drawn to a method of administering a composition comprising a nonviral, free DNA vector . . . ."); page 10, lines 20-21 ("In relation to the method of administering composition comprising a nonviral, free DNA vector . . . ."); page 16, first full paragraph ("Hence, one of skill in the Art at the time of the invention could not reasonably predict the use of any nonviral, nucleic acid molecule . . . . Further, a detailed study of the different non-viral gene transfer systems is required . . . ."); page 17, second full paragraph ("In relation to the use of non-viral gene transfer technology . . . ." and ""While viral vectors have evolved specific mechanisms for

> Nucleic acids and the corresponding encoded proteins of the markers of the present invention can be used therapeutically in a variety of modes. The nucleic acids and encoded proteins can be administered by any means known in the art. Such methods include, using liposomes, nanospheres, viral vectors, non-viral vectors comprising polycations, etc. Suitable viral vectors include adenovirus, retroviruses, and sindbis virus.

Thus, while the claimed method encompasses use of non-viral vectors, it is not limited to their use.

The state of the prior art and the predictability or unpredictability of the art

The Office Action devotes several pages to a discussion of prior art references it contends reflect the state of the prior art at the time the application was filed and describe various difficulties with achieving successful gene therapy:

- Orkin *et al.*, "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995 (Orkin);
- Goodman & Gilman's The Pharmacological Basis of Therapeutics, 1996;
- Marshall, *Science 269*, 1050-55, 1995 (Marshall);
- Verma & Sonyia, *Nature 389*, 239-42, 1997 (Verma);
- Zabner *et al.*, *J. Biol. Chem. 270*, 18997-19007, 1995 (Zabner); and
- Lechardeur *et al.*, *Gene Ther. 6*, 482-97, 1999 (Lechardeur).

Each of these references was published between 1995 and 1999. The state of the art of gene therapy in 1995-1999 is not relevant to whether the claimed method was enabled at this application's July 15, 2002 priority date. It is the state of the art in July 2002 that is relevant to

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release of viral DNA from endosomes, and mechanisms to gain entry across the nuclear pore complexes, the inability to overcome these limitations for successful nonviral gene transfer requires further developing and testing of the nonviral vectors.").

the enablement of claims 10 and 12-19. The following documents, which are listed in the accompanying Information Disclosure Statement, provide evidence that those skilled in the art in July 2002 were able to effectively transfer and express exogenous genes in neurons *in vivo*:

Auricchio *et al.*, "Exchange of surface proteins impacts on viral vector cellular specificity and transduction characteristics: the retina as a model," *Human Molecular Genetics 10*, 3075
Bankiewicz *et al.*, "Convection-enhanced delivery of AAV vector in parkinsonian monkeys; in vivo detection of gene expression and restoration of dopaminergic function using pro-drug approach," *Exp. Neurol. 164*, 2-14, July 2000 (abstract)
Biewenga *et al.*, "Plasmid-mediated gene transfer in neurons using the biolistics technique," *J. Neurosci. Methods 71*, 67-75, January 1997 (abstract)
Blesch *et al.*, "Modulation of neuronal survival and axonal growth in vivo by tetracycline-regulated neurotrophins expression," *Gene Therapy 8*, 954-60, June 2001 (abstract)
Besch & Tuszynski, "GDNF gene delivery to injured adult CNS motor neurons promotes axonal growth, expression of the trophic neuropeptide CGRP, and cellular protection," *J. Comp. Neurol. 436*, 399-410, August 2001 (abstract)
Blits *et al.*, "Pharmacological, cell, and gene therapy strategies to promote spinal cord regeneration," *Cell Transplant. 11*, 593-613, 2002 (abstract)
Boviatsis *et al.*, "Gene transfer into experimental brain tumors mediated by adenovirus, herpes simplex virus and retrovirus vectors," *Hum. Gene Ther. 5*, 183-91, February 1994 (abstract)
Breakefield & DeLuca, "Herpes simplex virus for gene delivery to neurons," *New Biol. 3*, 203-18, March 1991 (abstract)
Chen *et al.*, "HSV amplicon-mediated neurotrphin-3 expression protects murine spiral ganglion neurons from cisplatin-induced damage," *Mol. Ther. 3*, 958-63, June 2001 (abstract)
Cheng *et al.*, "Human immunodeficiency virus type 2 (HIV-2) vector-mediated in vivo gene transfer into adult rabbit retina," *Curr. Eye Res. 24*, 196-201, March 2002 (abstract)
Davar *et al.*, "Comparative efficacy of expression of genes delivered to mouse sensory neurons with herpes virus vectors," *J. Comp. Neurol. 339*, 3-11, January 1994 (abstract)
de Marco *et al.*, "MR imaging of gene delivery to the central nervous system with an artificial vector," *Radiology 208*, 65-71, July 1998 (abstract)
Di Polo *et al.*, "Prolonged delivery of brain-derived neurotrophic factor by adenovirus-infected Müller cells temporarily rescues injured retinal ganglion cells," *Proc. Natl. Acad. Sci. USA 95*, 3978-83, March 1998
Fathallah-Shaykh *et al.*, "Gene Transfer into Brain Parenchyma Elicits Antitumor Effects," *Cancer Res. 60*, 1797-99, April 1, 2000
Garcia-Valenzuela *et al.*, "Axon-mediated gene transfer of retinal ganglion cells in vivo," *J. Neurobiol. 32*, 111-22, January 1997 (abstract)
Haas *et al.*, "Single-cell electroporation for gene transfer in vivo," *Neuron 29*, 583-91, March 2001 (abstract)
Hagihara *et al.*, "Widespread gene transfection into the central nervous system of primates," *Gene Ther. 7*, 759-63, May 2000 (abstract)
Han *et al.*, "Transgene expression in the guinea pig cochlea mediated by a Lentivirus-derived gene transfer vector," *Hum. Gene Ther. 10*, 1867-73, July 20, 1999 (abstract)

Hecker *et al.*, "Nonviral gene delivery to the lateral ventricles in rat brain: initial evidence for widespread distribution and expression in the central nervous system," *Mol. Ther. 3*, 375-84, March 2001 (abstract)
Hossain *et al.*, "Human FGF-1 gene delivery protects against quinolinate-induced striatal and hippocampal injury in neonatal rats," *Eur. J. Neurosci. 10*, 2490-99, August 1998 (abstract)
Isenmann *et al.*, "Short communication: protection of axotomized retinal ganglion cells by adenovirally delivered BDNF in vivo," *Eur. J. Neurosci. 10*, 2751-56, August 1998 (abstract)
Johnston *et al.*, "Delivery of human fibroblast growth factor-1 gene to brain by modified rat brain endothelial cells," *J. Neurochem. 67*, 1643-52, October 1996 (abstract)
Joung *et al.*, "Effective gene transfer into regenerating sciatic nerves by adenoviral vectors: potentials for gene therapy of peripheral nerve injury," *Mol. Cells. 10*, 540-45, October 2000 (abstract)
Kaspar *et al.*, "Targeted retrograde gene delivery for neuronal protection," *Mol. Ther. 5*, 50-56, January 2002 (abstract)
Keir *et al.*, "Adeno-associated virus-mediated delivery of glial cell line-derived neurotrophic factor protects motor neuron-like cells from apoptosis," *J. Neuroviol. 7*, 437-46, October 2001 (abstract)
Knight *et al.*, "Non-viral neuronal gene delivery mediated by the H_C fragment of tetanus toxin," *Eur. J. Biochem. 259*, 762-69, 1999
Kugler *et al.*, "Transduction of axotomized retinal ganglion cells by adenoviral vector administration at the optic nerve stump: an in vivo model system for the inhibition of neuronal apoptotic cell death," *Gene Ther. 6*, 1759-67, October 1999 (abstract)
Lachman & Efstathiou, "Utilization of the Herpex Simplex Virus Type 1 Latency-Associated Regulatory Region To Drive Stable Reporter Gene Expression in the Nervous System," *J. Virol. 71*, 3197-207, April 1997
Lilley *et al.*, "Multiple Immediate-Early Gene-Deficient Herpes Simplex Virus Vectors Allowing Efficient Gene Delivery to Neurons in Culture and Widespread Gene Delivery to the Central Nervous System In Vivo," *J. Virol. 75*, 4343-56, May 2001
Liu *et al.*, "Application of recombinant adenovirus for in vivo gene delivery to spinal cord," *Brain Res. 768*, 19-29, September 12, 1997 (abstract)
Mandel *et al.*, "Nerve growth factor expressed in the medial septum following in vivo gene delivery using a recombinant adeno-associated viral vector protects cholinergic neurons from fimbria-fornix lesion-induced degeneration," *Exp. Neurol. 155*, 59-64, January 1999 (abstract)
Naldini *et al.*, "Efficient transfer, integration, and sustained long-term expression of the transgene in adult rat brains injected with a lentiviral vector," *Proc. Natl. Acad. Sci. USA 93*, 11382-88, October 1996 (presented at a conference held June 9-11, 1996)
Naldini *et al.*, "In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector," *Science 272*, 263-67, April 12, 1996 (abstract)
Palmer *et al.*, "Development and Optimization of Herpes Simplex Virus Vectors for Multiple Long-Term Gene Delivery to the Peripheral Nervous System," *J. Virol. 74*, 5604-18, June 2000
Schneider *et al.*, "Retargeting of adenoviral vectors to neurons using the Hc fragment of tetanus toxin," *Gene Ther. 7*, 1584-92, September 2000 (abstract)
Sinnayah *et al.*, "Selective Gene Transfer to Key Cardiovascular Regions of the Brain: Comparison of Two Viral Vector Systems," *Hypertension 39*, 603-08, 2002
Taylor, "Cell vehicles for gene transfer to the brain," *Neuromuscul. Disord. 7*, 343-51, July 1997 (abstract)

Terashima *et al.*, "Retrograde and anterograde labeling of cerebellar afferent projection by the injection of recombinant adenoviral vectors into the mouse cerebellar cortex," *Anat. Embryol. 196*, 363-82, November 1997 (abstract)
Wu *et al.*, "An AAV promoter-driven neuropeptide Y gene delivery system using Sendai virosomes for neurons and rat brain," *Gene Ther. 3*, 246-53, March 1996 (abstract)

The Office Action also spends several pages discussing various ways in which cell death can occur. The Office Action concludes that because "neuronal death is unlikely to have a single, discrete pathway," use of a nucleic acid molecule expressing a neuronal marker "to prevent a neurodegenerative disease" is unpredictable. First, as noted above, the claims do not require prevention of a neurodegenerative disease. Second, the specification teaches that expression of the recited neuronal marker proteins is specifically decreased after axiotomy (which causes neuronal cell death) and that administration of a nucleic acid molecule expressing the recited neuronal marker proteins can be used to reduce neuronal cell death. Understanding the mechanism by which any particular neuronal marker protein reduces neuronal cell death is neither relevant nor required for enablement.

The quantity of experimentation necessary, the amount of direction or guidance provided in the specification, and the presence or absence of working examples

The standard for whether a claim is enabled is whether any experimentation that must be carried out is undue. *Mineral Separation v. Hyde*, 242 U.S. at 270. However, this does not mean that no experimentation at all is permitted. Thus, even if routine experimentation were required to optimize the claimed methods, that does not make the experimentation undue:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 169 U.S.P.Q. 759 (2d. Cir. 1971), *cert. denied*, 404 U.S. 1018 (1972)]. The test is not merely quantitative, since a considerable

> amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. In re Rainer, 52 CCPQ 1593, 347 F.2d 574, 146 USPQ 218 (1965). Also see In re Colianni, [561 F.2d 220, 195 US.P.Q. 150 (C.C.P.A. 1977)].

Ex parte Jackson, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. Interf. 1982).

The specification is addressed to those skilled in the art. The law is clear that the specification need not provide knowledge that is generally known by those skilled in the art. Applicants can properly rely on common knowledge in the art to bolster and supplement the teachings of the specification. *Genentech Inc. v. Novo Nordisk A/S*, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). The specification and the references discussed above demonstrate that those skilled in the art at the July 2002 priority date of this application had a variety of tools available with which to successfully deliver to a target cell a nucleic acid molecule encoding a desired protein.

Finally, the Office Action faults the specification for not providing working examples. Working examples are not required to enable an invention. *In re Long*, 368 F.2d 892, 895, 151 U.S.P.Q. 640, 642 (C.C.P.A. 1966). In view of the extensive teachings in the prior art regarding *in vivo* gene transfer in general and the explicit teachings of the specification, the lack of *in vivo* working examples should not be given undue weight.

The level of skill in the art

The Office Action acknowledges that the level of skill in the art was high at the time the application was filed. This factor weighs in favor of enablement, especially when taken together with the teachings of the specification and prior art discussed above.

All the evidence of record must be considered in its entirety. *In re Oetiker*, 977 F.2d

1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). The Office has not properly weighed the evidence of record, including the relevance of the documents cited in the Office Action. When correctly analyzed, the weight of evidence of record in this application favors a finding of enablement of claims 10 and 12-19.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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